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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,357	11/24/2003	Michela Gallagher	JHV-028.01	4705

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EXAMINER	
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1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,357	GALLAGHER ET AL.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44 and 53* is/are pending in the application.

4a) Of the above claim(s) *1-43,45-52 and 54-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :3/21/07;8/10/05;5/13/05;10/19/04;9/2/04; 6/28/04;6/21/04.

DETAILED ACTION

Applicant's response to the Restriction/Election requirements, filed 3/21/07, electing with traverse Group XIII, and 2-propylpentanoate as the compound species, is acknowledged and made of record.

Restriction/Election requirement

Applicant contends that the restriction requirement should be withdrawn because the elected method claims specifically recite the use of a product of claim 38; therefore, the product claim should not be subject to restriction from the claimed process of Group XIII." Applicant also contends that there is no additional search burden to include claim 38 with claims 44 and 53.

Applicant's arguments are not deemed to be persuasive as the product claims are properly restricted from the method claims. To the extent that the claims encompass a multiplicity of different compounds, an undue search burden would be created if the product and method claims were searched together.

In the Office action, dated September 15, 2006, Group V was erroneously stated as comprising claims 33-36 and 33-44 (see page 1 of the Action). Group V is corrected to comprise claims 33-39, which are drawn to a pharmaceutical composition.

Status of the Claims

Claims 1-62 are pending in this application and are the subject of this Office action.

Claims 1-43, 45-52, and 54-62 are withdrawn for purposes of examination for being directed to non-elected subject matter.

Claims 44 and 53 are presented for examination.

Claim rejections – 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 44 and 53 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as valproic acid, which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 44 and 53 are directed to encompass compounds of formula II disclosed as related to valproic acid of the formula II in terms of optional groups (e.g. X , R, R1) (specification, page 26, paragraph 0288), which only correspond in some undefined way to specifically instantly disclosed chemicals. Also, applicant discloses compounds that modulate metabotropic glutamate receptor (mGluR) activity and compounds that modulate pituitary adenyl cyclase activator polypeptide (PACAP) expression; however, no structure-function data is disclosed that reasonably correlate with the contemplated therapeutic effect to be achieved in practicing the invention. Thus, none of these drugs meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly

variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus

because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim rejection under 112, first paragraph – Enablement

Claims 44 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods for screening compounds for utility in promoting cognitive function and preserving cognitive function in a rat, does not reasonably provide enablement for drugs , except ceftriaxone, for preserving cognitive function in certain mammals such as humans. This is a scope enablement rejection.

Applicant discloses the unexpected discovery regarding the reduction of L-glutamate levels in the extracellular space surrounding neurons and glial cells in the brain, including the synpatice cleft and extrasynpatic space, correlates with preservation or promotion of cognitive function (specification, page 82, last paragraph to page 83, line 5). Applicant discloses that lidociane can increase expression or activity of glutamate transporter proteins; kinase inhibitors are disclosed as having this said effect (specification, page 83, second to last paragraph. Applicant discloses that prodrugs of the compounds of formula I, II, and III are included in the methods of the invention (specification, page 88, first full paragraph).

Applicant discloses that normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration (specification, page 93). Applicant discloses that compounds used in the

methods should readily penetrate the blood-brain barrier when peripherally administered; compounds which cannot penetrate the blood-brain barrier can still be effectively administered directly into the central nervous system e.g. by intraventricular route (page 93, last paragraph).

Applicant discloses that behavioral tests were performed on 9 young (4-6 mo) and 18 aged (25-27 months) pathogen free male Long-Evans rats with the MWM, followed by training and testing in the RAM to assess test-retest reliability for individual differences in cognitive function across the two tasks (page 95, second to last paragraph). Applicant exemplification of the effects of ceftriaxone on GLT1 mRNA in young rats is disclosed; the drug was administered at 200 mg/kg intramuscularly to young rats for one week (page 110). Applicant discloses that the hippocampal tissue, found in the temporal cortex, includes the subiculum, dentate gyrus, and areas known as Ca1, CA2, CA3, and CA4 (page 8, paragraph 0074, lines 5-9). Applicant discloses that the hippocampus is involved in processes such as short-term memory, the formation of long-term memory, memory retrieval, declarative memory and spatial navigation (page 8, paragraph 0074, lines 9-12).

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method for reducing tumor burden in patients suffering from cancers in which the cancer cells express CCKβ/gastrin receptor and little or no EGFR.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for physiological activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the mode of action of central nervous system acting drugs is often unknown or very unpredictable and administration of such agents is often accompanied by undersirable effects. Although drugs may be administered directly into the brain via intraventricular injection, administration of drugs via other routes of administration often varies widely depending on the particular route of administration and liphophilicity of the administered drug. This variability often affects drug availability in the brain, which may reasonably affect the therapeutic responsiveness of brain cells. Besides, there is a disproportionately sparse number of discovery of new and predictable curative drugs for treating central nervous system diseases and diseases related to aging compared with the vast number of new drugs discovered. To the extent that the cognitive abilities of humans is reasonably considered to be of high order as compared to rodents, one skilled in the art would not

be able to predictably extrapolate the disclosed teachings of the claimed invention to humans without undue experimentation.

2. The breadth of the claims

The claims are relatively broad. Claim 1 is drawn to a method of preserving cognitive function in a mammal. Applicant discloses that "[p]reserving" cognitive function refers to affecting normal or impaired cognitive function such that it does not decline or does not fall below that observed in the subject upon first presentation or diagnosis, e.g., to the extent of expected decline in the absence of treatment. Thus, the invention reads on any subject regardless of age, including healthy mammals of any age. Because the therapeutic response to be achieved would necessarily vary depending upon the mammalian species treated and the age of the mammal, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (dosages, timing, administration routes etc.) necessary to treat certain mammals, including humans. The 'working examples" are limited to in vitro studies and in vivo rat studies. Thus, the applicant at best has provided specific direction or guidance only for a general administration protocol for screening drugs and a method of treating cognitive function in a rat. No reasonably specific guidance is provided concerning useful therapeutic protocols or specific agents for preserving cognitive function in other mammals.

4. The quantity of experimentation necessary

Based on the above, it is reasonable to surmise that the level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention in preserving cognitive function certain mammals, including humans. Thus, based on the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for preserving cognitive function in the absence of evidence to the contrary.

For the reasons stated above, claims 44 and 53 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claims 1, 7-10 are anticipated by Sun et al. as Sun et al disclose administering An identical active agent i.e. 5(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)-amide, to a subject using the claimed method steps. Accordingly, inhibition or control of angionesis would be inherent

Claim rejection under 102(e)

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 44 and 53 are anticipated by Ohuchida et al (US Patent 7, 176, 240 B2).

Ohuchida et al. (US Patent 7,176,240 B2) teach pentanoic acid derivatives are potentially useful in improving the GABAa receptor responses (column 3, lines 53-61; columns 7-8). Ohuchida et al teach, for example, 2-propylpentanoic acid, known as valproic acid, and 2-propylpentanamide, which is also known as valpromide; both agents are antiepileptic drugs (column 3, line 66 to column 4, line 38). Formula II of the instant application also overlaps other pentanoic acid derivatives taught by Ohuchida et al. e.g. 2-ethylhexanoic acid, 2-propylhexanoic acid, 2-propyldecanoic acid (column 3, line 67 to column 4, line 67). Ohuchida et al. also teach that these pentanoic acid derivatives and non-toxic salts and acid addition salts thereof are useful for prevention and/or treatment for neurodegenerative disease (Alzheimer's disease etc.) and neuronal dysfunction by stroke or traumatic injury (multiple sclerosis etc.) (abstract). Ohuchioda et al. disclose that abnormalities in the astrocyte may be the determinant factors in inducing various brain-related diseases (column 2, lines 17-19). In view of applicant's disclosure that there are many conditions, such as dementias (e.g. Lewy body dementia, vascular dementia, Alzheimer's Diseases, and HIV associated dementia), Huntington's Disease, Parkinson's Disease, schizophrenia, depression, amyotrophic lateral sclerosis, Mild Cognitive Impairment (MCI) and Age Related Cognitive Decline (ARVD), of which sensitive detection of cognitive impairment would benefit the sufferer of the condition, the instant application and the reference overlap with respect to the treatment groups and the actual treatment using pentanoic acid derivatives. Thus, the instant claims are anticipated by Ohuchida et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 8 a.m. to 4:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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29 April 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER